Der perkutane Aortenklappenersatz - Aufbruch in eine neue Ära

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Transcatheter Aortic Valve Implantation

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Contents

1. Introduction

The introduction of this cumulative habilitation thesis will provide a background of the nature and prognosis of aortic valve stenosis. Treatment options of aortic stenosis will be discussed and the development of transcatheter aortic valve implantation (TAVI) will be reviewed. Furthermore, previous research is summarized and a list of open questions and areas of research are provided.

1.1. Aortic stenosis

Aortic stenosis occurs due to calcific degeneration of a tricuspid or bicuspid valve, or due to rheumatic heart disease. Calcific aortic stenosis is the most frequent cause of valvular heart disease in the Western world, and the leading indication for operative valve replacement. The prevalence of aortic stenosis increases with age and reaches almost 5% in patients ≥ 75 years (Figure 1)[1]. Aortic stenosis is a mechanical problem that requires a mechanical solution. If treated with medical therapy only, patients experience a high rate of death[2, 3].

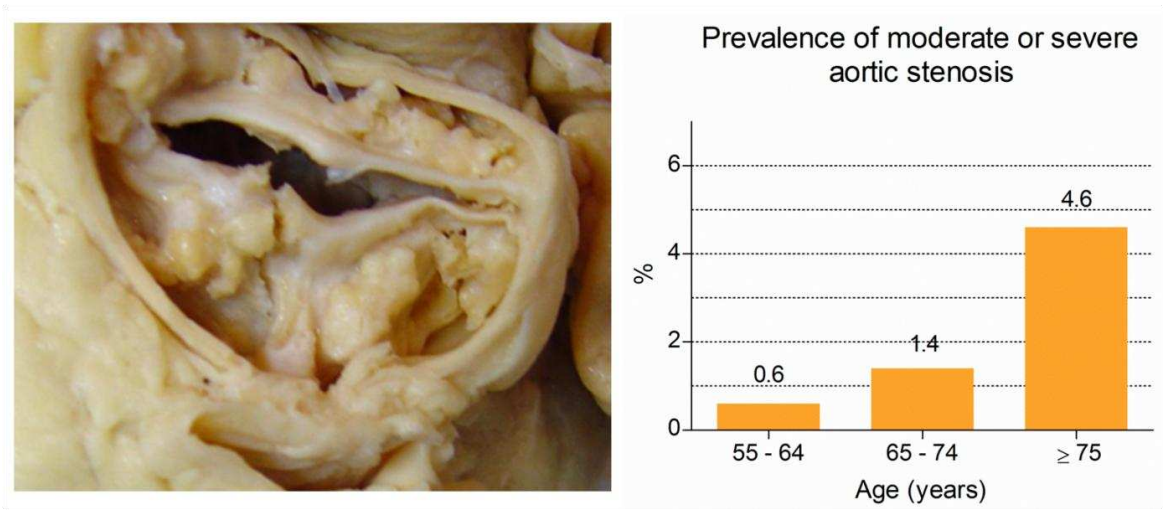

Figure 1. A severely calcified and stenotic aortic valve (left). The prevalence of moderate or severe aortic stenosis increases with age (right).

Surgical aortic valve replacement improves both symptoms and survival in patients with severe stenosis; but with advanced age, poor left ventricular function, or comorbidities, operative risk may be high or even prohibitive[4, 5]. A survey of European hospitals in 2001

found that surgery was not offered in 10% of patients with severe aortic stenosis[6]. In addition, many elderly patients refuse to undergo open heart surgery. As aconsequence, during the last decade, transcatheter aortic valve implantation (TAVI) has emerged as an alternative, less invasive treatment option in such patients[7, 8].

1.2. A brief history of TAVI

The search for less invasive treatment options for patients with valvular heart disease was pioneered by Hywel Davies in 1965. Davies developed a parachute-like valve to treat aortic regurgitation. The valve was placed in the descending aorta and offered little resistance to the systolic blood flow in antegrade direction, but passively opened during diastole to obstruct the retrograde diastolic flow[9]. However, such valves were never utilized in humans.

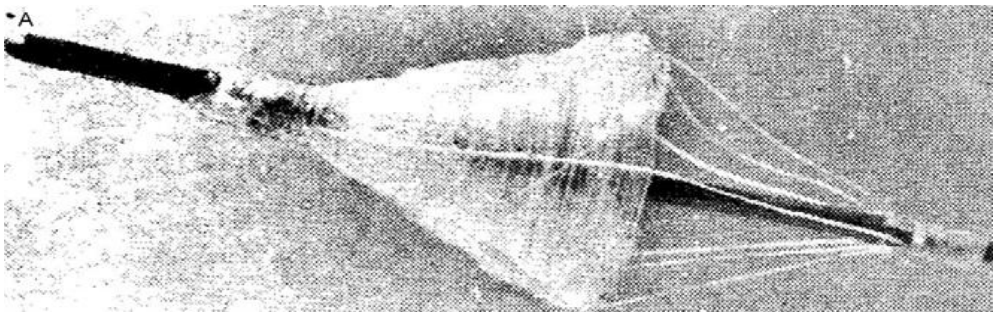

Figure 2. In 1965, Hywel Davies implanted a parachute-like valve in the descending aorta of a dog. The valve was intended to treat patients with aortic regurgitation but was never utilized in humans.

In 1985, Alain Cribier performed the first aortic balloon valvuloplasty, which was the first catheter-based intervention specifically designed to treat non-operable calcific aortic stenosis[10]. At that time, age > 75 years per se was often a contraindication to aortic valve replacement. After rapid adoption of balloon valvuloplasty and explosive growth worldwide, the lack of survival benefit and the high recurrence rate of severe stenosis led to a marked decline in its use[11].

In 1989, Henning Andersen developed a balloon expandable aortic valve that could be implanted percutaneously in a porcine model[12], but he did never use this technique in humans. The first in human transcatheter valve implantation was performed by Philip Bonhoeffer in 2000. He implanted a stented valve made of a bovine jugular vein into a pulmonary artery conduit of a young patient with congenital heart disease.

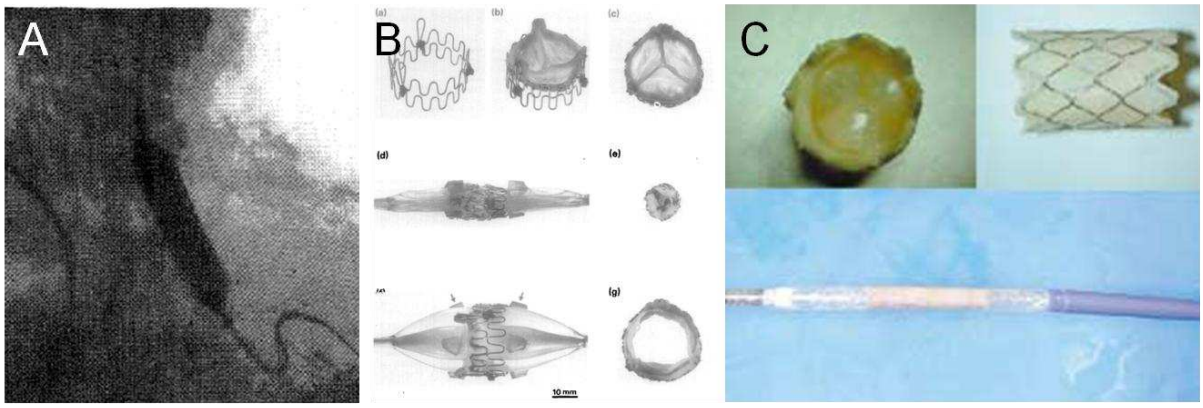

Figure 3. In 1985, the first balloon aortic valvuloplasty was performed by Alain Cribier in Rouen, France (A). Four years later, Henning-Rud Andersen implanted a balloon expandable valve within a porcine model (B). The first in man transcatheter valve implantation was performed 2000 by Philip Bonhoeffer in Paris utilizing a valve made of a bovine jugular vein (C).

Soon after the development of aortic balloon valvuloplasty, Alain Cribier started working on a stent that could deploy an aortic valve in patients with calcific stenosis, regardless of the amount of calcification[11]. It took 9 years of development and animal trials until the first-in-man implantation of a transcatheter aortic valve could be successfully performed on April 16th, 2002 by Alain Cribier in Rouen, France. Cribier implanted a 23 mm balloon-expandable transcatheter heart valve in a patient with severe heart failure and multiple comorbidities utilizing an antegrade transseptal approach through the femoral vein.

The retrograde transfemoral arterial access with a balloon expandable valve was later developed and standardized in Vancouver by John Webb in 2005[13]. This approach allowed a higher technical success rate, although there was an initial learning curve with a relatively high rates of vascular complications. At the same time, Eberhard Grube and Jean-Claude Labordé started implanting a self-expanding valve with porcine pericardial tissue leaflet, the CoreValve[14].

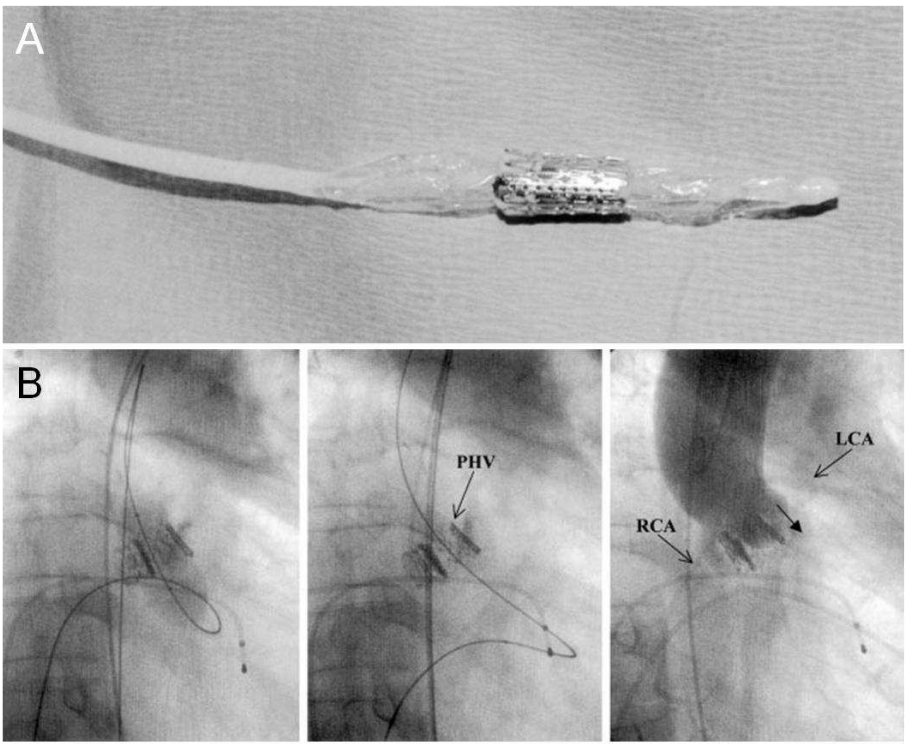

Figure 4. Alain Cribier developed a balloon expandable bovine valve on a cobalt chromium alloy stent (A). The first-in-man transcatheter aortic valve implantation was performed in 2002 utilizing an antegrade transvenous approach (B).

With the initial high profile catheters and sheaths, not all patients could be treated through the femoral arteries. In 2006, Sam Lichtenstein, a cardiac surgeon from Vancouver, performed the first transapical TAVI through a left-sided mini thoracotomy. During the following years, other alternative access routes were developed including the transaxillary/subclavian access, the direct aortic access, and even a transcarotid access. In Switzerland, the first TAVI was performed in 2007. It is estimated that as of 2012, about 100'000 TAVI procedures have been performed worldwide.

Figure 5. Pioneers in transcatheter aortic valve implantation. From left to right: Alain Cribier, John Webb, and Eberhard Grube.

1.3. Summary of previous research

After Cribier et al. had reported the short-term outcome of their first 6 patients in 2004 utilizing the antegrade transvenous approach[15], Webb et al. and others reported their experience with the retrograde transarterial access[13, 14, 16-21]. From these early transarterial case series, it became evident that vascular complications were one of the limiting factors of transarterial transfemoral TAVI. These complications included dissection or rupture of the iliac and femoral arteries, the aorta, and the aortic annulus and were reported in up to 30% of patients undergoing TAVI with the early high profile catheters requiring 22-24 F sheaths. In an attempt to reduce iliofemoral complications, a surgical cut-down to expose and control the iliofemoral artery above and below the puncture site was initially performed [8, 13, 14, 16, 21-23]. Later, operators started utilizing percutaneous closure devices to reduce the invasiveness of the procedure and allow earlier patient ambulation[18-20, 24-26].

Another problem that was recognized very early were paravalvular leaks. Cribier noted in his first publication that 2/6 patients had severe paravalvular aortic regurgitation (PAR) following TAVI[15]. Subsequent publications reported moderate or severe PAR in 8-22%. Patients with acute severe PAR often developed cardiogenic shock, but the relevance of moderate or mild PAR was less clear. It was known that there were different mechanisms that caused PAR. Undersizing of transcatheter valves was the most frequent cause, but malpositioning (too low or too high), or severe calcification were other causes. Before 2010, valves were selected based on a single measurement of the annular diameter on transthoracic or transesophageal echocardiography[27]. However, the annulus is a complex, three-dimensional, nearly uniformly oval shaped structure[28]. To measure the annulus in its true plane, a three-dimensional imaging modality appeared necessary, but it was unknown if such a strategy will truly lead to less PAR. Furthermore, there was a concern that larger valves may increase the risk for annular rupture.

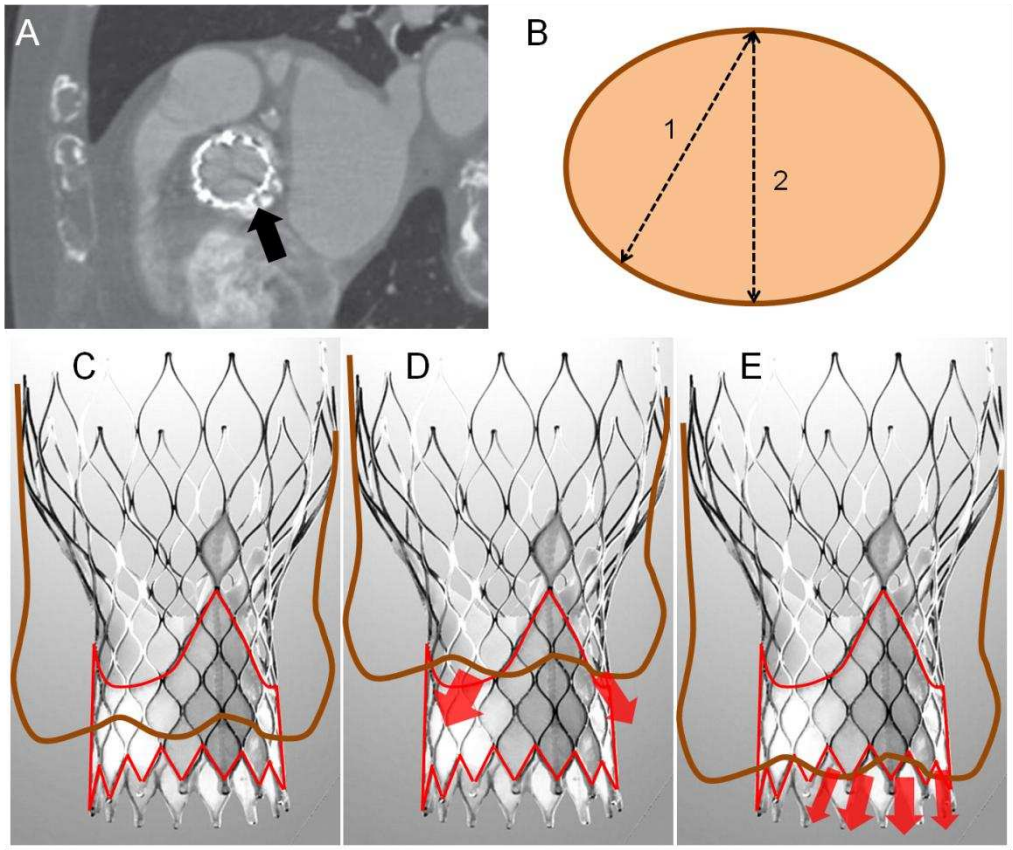

Figure 6. Mechanisms of paravalvular regurgitation. Heavily calcified leaflets may prevent complete sealing (A, arrow). The potential hazards hazards of 2-dimensional imaging techniques for measurements of a 3-dimensional, oval structure is demonstrated in B. The true annular diameter is underestimated in both measurements (arrow 1, tangential measurement, arrow 2, measurement of the short axis). C shows a correctly positioned CoreValve. Paravalvular regurgitation (red arrows) may result from too low (D) or too high (E) implantation.

Initially, the rate of cerebrovascular events during and after TAVI ranged between 2-6%, although definitions did vary[13, 16, 18-21, 29, 30]. However, it was the publication of the PARTNER A trial that made the risk for strokes one of the hot research topics in TAVI[7]. In this trial, the rate of cerebrovascular events (including major strokes, minor strokes, and transient ischemic attacks) was higher in the TAVI group than in the surgical group, although the rates of strokes (4.6% vs. 2.4% at 30 days) did not differ significantly. Periprocedural strokes may result from embolization of calcified microdebris during positioning and deployment of the valve, but also during passage through the aortic arch with the guidewire and the catheter, during balloon valvuloplasty, or re-capture of a valve . Not infrequently, strokes occurred during the first 1-2 days after the procedure. These postprocedural stroke may be due to the non-endothelialised and thrombogenic bioprosthesis itself, new-onset atrial fibrillation, late calcific embolism, or possibly due to late thrombosis or hemorrhage following earlier embolism.

1.4. Unsolved issues and open questions

After the pioneering initial use of TAVI proofing its feasibility, several open questions remained:

- Patient selection
- Vascular complications
- Valve sizing and paravalvular regurgitation
- Cerebrovascular events
- Need for a permanent pacemaker
- Safety and efficacy of next-generation valves
- Long-term outcome and valve durability

Figure 7. Currently, the two most frequently implanted valves include the Edwards SAPIEN XT (Edwards Lifesciences, Irvine, USA) and the Medtronic CoreValve (Medtronic Inc., Minneapolis, USA).

The research presented and discussed in this cumulative habilitation thesis aims to answer some of these open questions. The research addressing such issues was performed at St. Paul's Hospital, University of British Columbia, Vancouver, Canada. Some of the projects were done in collaboration with other centers such as the Québec Heart and Lung Institute, Québec City, Canada, the Cleveland Clinic, Cleveland, USA, and Aarhus University Hospital, Aarhus, Denmark.

First, the relevance of concomitant mitral regurgitation in patients with severe aortic stenosis undergoing TAVI was investigated (**Toggweiler** et al., *J Am Coll Cardiol* 2012). We showed that women may be excellent candidates for TAVI (**Humphries**, **Toggweiler** et al., *J Am Coll Cardiol* 2012). Then, the role of annular measurements with computed tomography for valve sizing protocols and their impact on the reduction of paravalvular regurgitation after TAVI was investigated (**Willson** et al., *J Am Coll Cardiol* 2012). Predictors for vascular complications, initially the most feared complication in TAVI, were then identified and their importance for patient selection and complication rates defined (**Toggweiler** et al., *J Am Coll Cardiol* 2012). Finally, five year outcome of TAVI was for the first time evaluated (**Toggweiler** et al., *J Am Coll Cardiol* 2012).

2. Patient selection: TAVI in specific patient subgroups

Typically, patients that are currently selected for TAVI are more than 80 years old, and have comorbidities such as coronary artery disease, diabetes, a prior stroke, chronic pulmonary disease, or kidney disease. These restrictions are applied more rigidly in North America than in other part of the world. Across Europe and especially in Germany, there is a trend towards TAVI in lower (intermediate) risk patients. Multicenter trials randomizing such patients vs. open heart surgery are under way (PARTNER 2, ADVANCE). With the current high-risk patients, studies with follow-ups beyond 2 years have shown that the median time of survival after TAVI is about 3 years[31]. Subgroup analyses of the PARTNER trial have demonstrated that long-term survival is mainly determined by (non-cardiac) comorbidities[32]. Therefore, TAVI should not be performed in the presence of relevant comorbidities that limit survival to less than 2-3 years. It is now generally recommended that each patient should be discussed and selected by a multidisciplinary Heart Team including cardiologists and cardiac surgeons. However, there are certain subgroups of patients that may benefit more from TAVI than others. Two of these subgroups may be patients with concomitant mitral regurgitation and women.

2.1. TAVI in patients with concomitant mitral regurgitation

Concomitant mitral regurgitation (MR) is present in most patients with severe aortic stenosis. The reported prevalence of moderate or severe MR in patients undergoing surgical aortic valve replacement ranges from 13% to 75%. Traditionally, patients with severe aortic stenosis and concomitant severe MR have been treated with surgical aortic valve replacement and mitral valve reconstruction or replacement. Patients with severe aortic stenosis and concomitant mild or less MR have been treated with aortic valve replacement only. The situation is less clear in patients with severe aortic stenosis and moderate MR. In contrast to surgical aortic valve replacement concurrent mitral valve repair or replacement has not been an option in patients undergoing TAVI, although new transcatheter mitral therapies such as the Mitraclip (Abbott Vascular, Illionois, USA) may offer options in future[33].

To better define the role of MR for outcome after TAVI, we tried to address the following clinical questions:

- What is the impact of MR on outcome after TAVI?
- Does MR improve after TAVI?
- Are there certain factors that predict improvement?

A total of 451 patients undergoing TAVI with a balloon expandable valve (Cribier Edwards, Edwards SAPIEN, and Edwards SAPIEN XT, all Edwards Lifesciences, Irvine, USA) at St. Paul's Hospital, Vancouver, British Columbia, and at the Quebec Heart and Lung Institute, Quebec City were analyzed[34]. MR at baseline was ≤ mild in 319 patients (71%), moderate in 89 (20%) and severe in 43 (10%). Patients with moderate or severe MR were older, were more often in atrial fibrillation, had more often a prior myocardial infarction, a lower ejection fraction, a smaller aortic valve area, and a higher Society of Thoracic Surgeons' (STS) risk score.

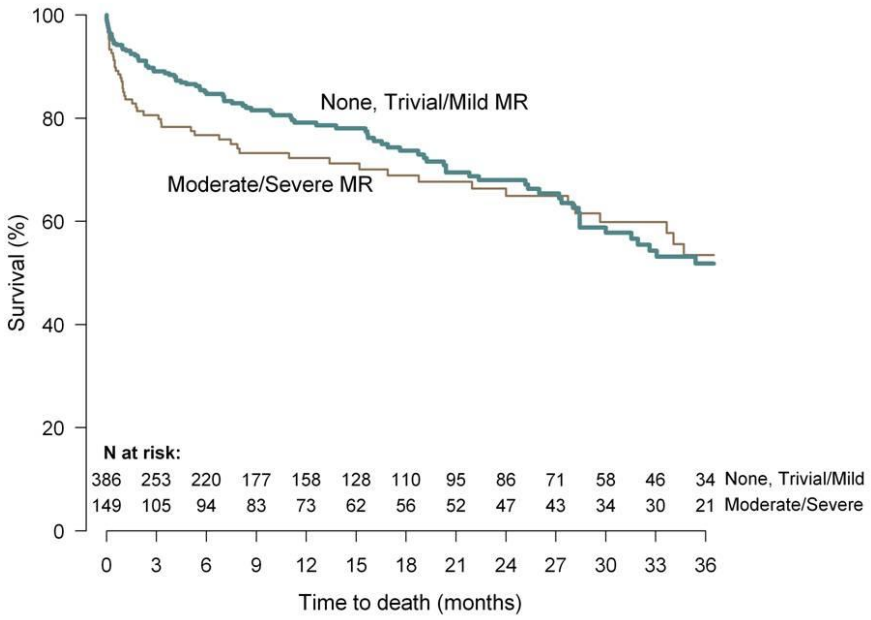

Figure 8. Kaplan-Meier curves for all-cause mortality in patients with none, trivial or mild MR and moderate or severe MR at baseline. (Toggweiler et al., *J Am Coll Cardiol* 2012;59:2068-2074)

Compared to patients with none, trivial or mild MR, patients with moderate/severe MR had a higher mortality rate during the first 30 days (unadjusted hazard ratio (HR) 2.04, 95% confidence interval (CI) 1.11 – 3.74, p = 0.02; adjusted HR 2.10, 95% CI 1.12 – 3.94, p = 0.02) but no difference after 30 days (unadjusted HR 0.94, 0.58 – 1.51, p = 0.80; adjusted HR

0.82, 0.50 – 1.34, p = 0.42). Therefore, moderate or severe MR was associated with an increased early, but not late mortality.

Since the severity of MR depends primarily on regurgitant orifice area and the systolic pressure gradient between the left ventricle and the left atrium, MR is expected to improve immediately after TAVI and may improve further in the mid- and long-term should positive left ventricular remodeling occur[35, 36]. Indeed, in our study, we observed that a few days after TAVI, MR improved in 61% of the patients with moderate or severe MR at baseline, and rarely worsened. At 1 year follow-up MR had improved in 55%, remained unchanged in 16%, and worsened in 1%; the remaining 28% had died.

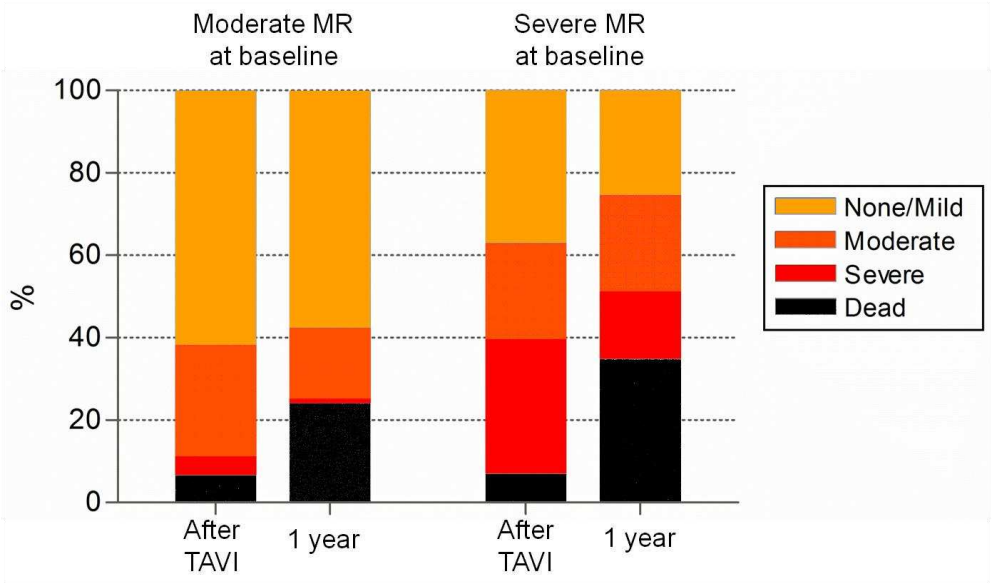

Figure 9. The degree of mitral regurgitation (MR) post TAVI and at 1 year follow-up in patients with moderate or severe mitral regurgitation at baseline. (Toggweiler et al., *J Am Coll Cardiol* 2012;59:2068-2074)

As expected, multivariable predictors of improved MR at 1 year (vs. unchanged MR, worse MR or death) were a mean aortic transvalvular gradient ≥ 40 mmHg, functional (as opposed to structural) MR, the absence of pulmonary hypertension, and the absence of atrial fibrillation. Indeed, a higher mean aortic transvalvular gradient at baseline results in a greater drop in afterload after TAVI and therefore also in a greater reduction of MR. In case of a positive left ventricular remodeling, patients with functional MR may improve even more. Pulmonary hypertension has been identified as a predictor of mortality and adverse outcome in previous studies. Finally, atrial fibrillation may worsen MR due to atrial and annular enlargement.

The randomized Placement of Aortic Transcatheter Valves (PARTNER) study suggested that patients with moderate or severe mitral regurgitation may derive a larger benefit from TAVI compared to both medical management and surgical aortic valve replacement[7, 8]. In the PARTNER B study, subgroup analysis showed that the number needed to treat to prevent 1 death at 1 year was 3 in patients with moderate or severe MR versus 7 in patients without it. In the PARTNER A study, 1-year mortality of patients with moderate or severe MR was 24.2% after TAVI (similar to the 27.7% in our study) and as high as 35% after surgical aortic valve replacement.

In conclusion, patients with severe aortic stenosis and concomitant moderate or severe MR have a very poor prognosis, if treated with medical therapy. Procedural mortality is increased in patients with advanced MR. Nevertheless these findings demonstrate late functional benefit in survivors and are consistent with (but do not prove) a possible late survival benefit. MR improved in over one half of patients at 1-year follow-up due to the combination of a reduced afterload and a positive remodeling. Improvement was more likely in patients with a high aortic transvalular gradient, functional MR, without pulmonary hypertension and without atrial fibrillation. Thus, such patients with severe aortic stenosis and concomitant moderate or severe MR may be ideal candidates for isolated treatment of aortic valve disease.

2.2. TAVI in women

In the PARTNER trial, a pre-specified subgroup analysis suggested that women benefit more from TAVI than men do[7]. Two additional publications examined sex differences in outcomes after TAVI. One found no difference in mortality at 30 days and 1 year after TAVI[37]. One study analyzing 260 consecutive patients reported better 1-year survival in women, but failed to adjust for baseline characteristics, which varied substantially between men and women[38].

In light of limited and conflicting evidence, we aimed to answer the following questions:

- Are there difference in baseline characterics between men and women?
- Does periprocedural outcome differ between men and women?
- Is there a difference in long-term survival?

We evaluated 641 consecutive patients (51% women, 49% men) who underwent TAVI at St. Paul's Hospital, Vancouver, Canada, and at the Québec Heart and Lung Institute, Québec City, Canada[39].

We found that women had higher mean aortic gradients, worse renal function, more often a porcelain aorta, and a better left-ventricular systolic function than men. Women were more often frail, while coronary artery disease, a prior myocardial infarction, prior percutaneous revascularisazion and chronic obstructive pulmonary disease (COPD) was more frequently present in men.

We made the following observations regarding procedural outcome:

- Women had more vascular complications
- Women had more life-threatening bleeds
- Women required more blood transfusions
- Despite these adverse events, the (adjusted) female odds ratio for 30-day mortality was 0.39 (95% CI 0.19 – 0.80)

This 30 day survival advantage was maintained up to 2 years:

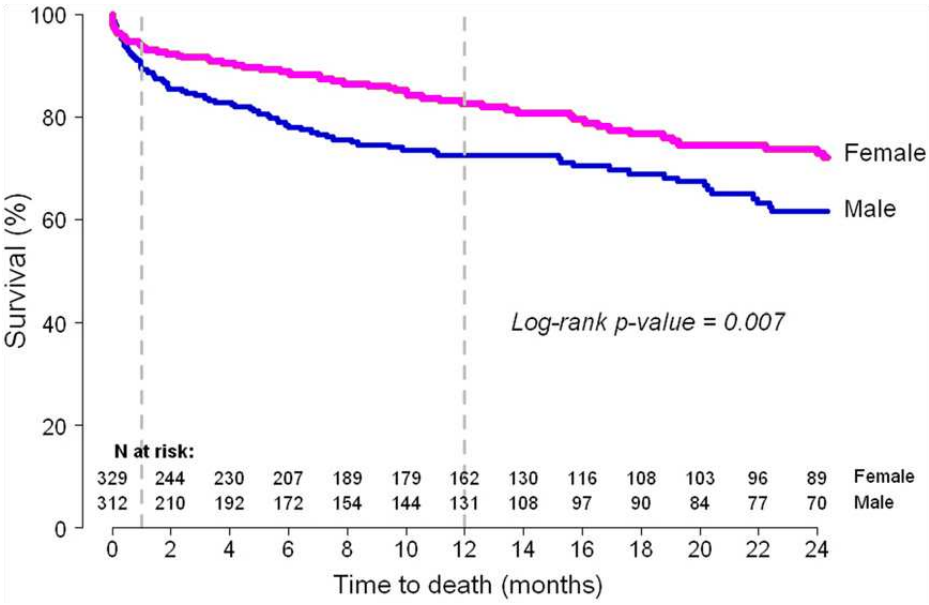

Figure 10. Women's survival advantage after TAVI throughout the 2-year follow-up period. (Humphries et al., J Am Coll Cardiol 2012;60:882-886.)

The reason for these findings remains unclear. It is unlikely that the survival advantage can be explained by the difference in baseline characteristics such as coronary artery disease. Also, the higher post-procedural complication rate may increase short- and mid-term mortality. One possible explanation may be the fact that interstitial fibrosis is more pronounced in male hearts with severe aortic stenosis, as is collagen I, II, and matrix metalloproteinase expression[40, 41]. Lower levels of fibrosis in women might lead to more rapid reversal of myocardial hypertrophy after correction of aortic stenosis[42]. Another explanation for the survival advantage might be the higher life-expectancy of women. However, the Kaplan Meier figure shows that the curves separate during the first 6 months and are parallel thereafter. The reason for this early survival advantage despite the higher periprocedural complication rate remained unclear.

3. Measurement of the aortic annulus and valve sizing

While during open heart surgery the aortic annulus can be directly inspected and sized, TAVI operators depend on external, indirect measurements of annular size. However, correct sizing of the annulus and choice of prosthesis is of utmost importance in order to avoid paravalvular leakage, device embolization, and annular rupture. Studies have shown that about 10-20% of patients are left with moderate or severe paravalvular regurgitation after TAVI and this has been associated with increased morbidity and mortality in several independent publications[43-45].

During the early experience with TAVI, the annulus was measured with 2-dimensional echocardiography using the parasternal long-axis view durig transthoracic echocardiography (TTE) or with transesophageal echocardiography (TEE) in the ~130° view. However, it is well known that the annulus is an oval structure where the long axis is in average 5-6 mm (about 20%) longer than the short axis[46, 47]. Therefore, measuring an oval-shaped annulus in only one dimension may under- or overestimate it's true size.

On the other hand, multidetector computed tomography (MDCT) offers a 3-dimensional to echocardiography and allows reconstruction of the aortic annulus in it's true plane. Utilizing MDCT for annulus measurements, we aimed to address the following questions:

- Does valve sizing according to MDCT annular measurements result in lower rates of paravalvular regurgitation?
- How should MDCT be integrated into valve sizing protocols?

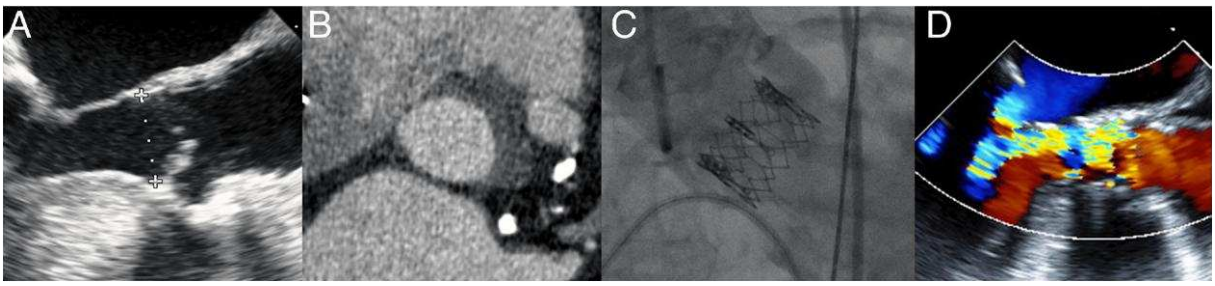

Figure 11. In a 82 year old patient, a 23-mm Sapien XT (Edwards Lifesciences, Irvine, California) valve was selected based on a TEE annular diameter of 22 mm (A). The MDCT mean annular diameter was 25 mm (22 x 28 mm) and area 4.90 cm2. The THV was undersized by 2 mm relative to the mean diameter and by 15% relative to the annular area (B). The THV appeared undersized on aortic root angiography (C). The patient had moderate to severe paravalvular regurgitation on echocardiography (D).

3.1. MDCT based annular measurements

We analyzed a total of 109 consecutive patients who underwent MDCT before TAVI at 2 centers, St. Paul's Hospital, Vancouver, Canada and Aarhus University Hospital, Aarhus, Denmark. Annular size was measured by TEE and MDCT. Valve size was chosen based on TEE measurements. A subset of patients (n = 50) also underwent MDCT before discharge to assess post-implant geometry of the balloon-expandable valves[47].

In our study, there was no patient with annular rupture, although this has been a concern when oversizing balloon expandable valves. The mean MDCT mean annular diameter was 23.9 ± 2.4 mm which was significantly larger than the mean TEE annular diameter (22.5 ± 1.9 mm, $p < 0.01$).

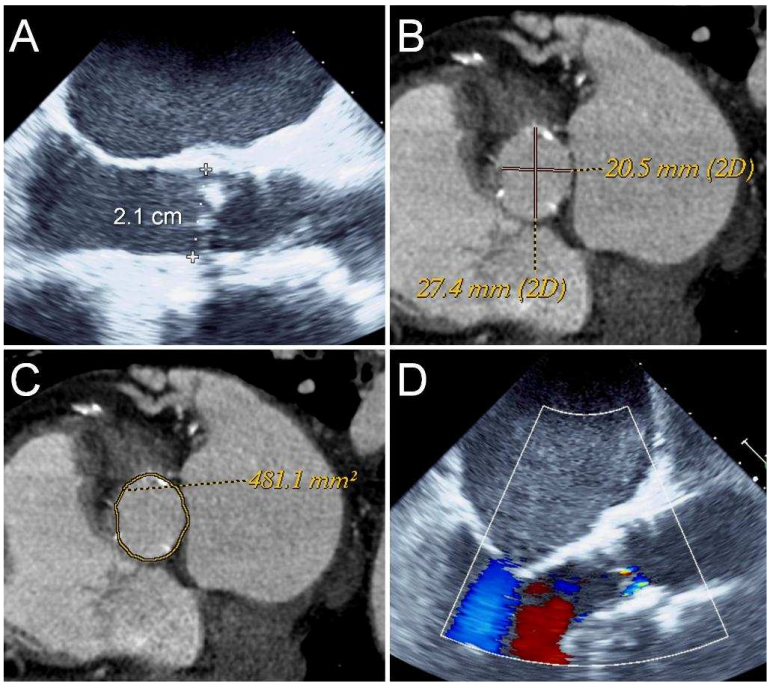

Figure 12. In a 79 year old patient TEE measured an annulus of 2.1 cm suggesting a 23 mm Edwards SAPIEN or a 26 mm Medtronic CoreValve (A). CT angiography measured an area of 481 mm2 (C) and a mean diameter of 24 mm (B) suggesting a 26 mm Edwards SAPIEN or a 29 mm Medtronic CoreValve valve with ~10% oversizing. A 26 mm Edwards SAPIEN valve was implanted with trace paravalvular leak (D).

Undersizing the nominal diameter or area of the valve relative to the MDCT measurements resulted in significantly more moderate or even severe paravalvular regurgitation. MDCT diameter (area under the curve (AUC) 0.81) and area (AUC 0.80) were more predictive of moderate or severe paravalvular regurgitation than TEE annulus diameter (AUC 0.70). For

patients with a valve diameter – mean annulus diameter < 1 mm, the incidence of moderate or severe paravalvular regurgitation was 21.4% vs 2.2% when the difference was ≥ 1 mm. For patients with a nominal area < 10% greater than the annular area, the incidence of moderate or severe paravalvular regurgitation was 19.1% vs. 0% when the nominal area was > 10% above the annular area.

Our results indicate that CT annular measurements have a good predictive value of moderate or severe paravalvular regurgitation following TAVI. Two-dimensional TEE measurements did often underestimate the true annular size. Our results therefore suggest that when utilizing CT measurements for valve sizing, the valve should be oversized by 10% relative to the measured area and by 1 mm relative to the mean diameter.

Based on these results, we published sizing recommendations for balloon expandable valves with the goal to oversize the valve relative to the measured area by 10-15%[48].

4. Predictors and relevance of vascular complications

Vascular complications are a major limiting factor when utilizing the large sheaths and catheters required for TAVI. For example, the rigorously monitored randomized PARTNER 1B trial that used the large 22- and 24 F sheaths reported major vascular complications in 30.7% of patients. Depending on its severity, vascular complications are associated with relevant mortality and morbidity[49]. Most studies have used non-standardized definitions and thus have yielded a wide range of vascular complication rates. In an attempt to allow direct comparison between clinical trials, the Valve Academic Research Consortium (VARC) has proposed standardized definitions for clinical endpoints[50, 51] which have recently been revised[52, 53].

Based on these data, we aimed to address the following issues with our research project:

- Evaluate the frequency and type of vascular complications in patients undergoing TAVI using current techniques and equipment
- Identify predictors for vascular complications

In this single-center study, we analyzed 137 patients undergoing percutaneous transfemoral TAVI at St. Paul's Hospital, Vancouver, British Columbia. All patients were evaluated with fluoroscopy and most also with CT angiography. Vascular and bleeding complications were defined according to the VARC and occurred in 24 patients (18%), major vascular complications in 5 (4%). We identified 3 predictors for vascular complications:

- Sheath size > minimal arterial diameter (as assessed by fluoroscopy and CT angiography)
- Moderate or severe calcification of the iliofemoral arteries as assessed by CT angiography
- Operator's experience

The rate of vascular complications was higher when the minimal artery diameter was smaller than the external sheath diameter (24% vs. 10%, p = 0.03), in the presence of moderate or severe calcification (29% vs. 9%, p = 0.03). The rate of vascular complications fell from 32% to 9% during the study period indicating a learning curve. We also showed that major

vascular complications were associated with a 30 day mortality rate of 20% and that the duration of hospital stay was more than twice as long as without complications.

Transfemoral access is considered the access of choice due to its least invasive nature and is feasible in the majority of patients undergoing TAVI. Most interventional cardiologists are very familiar with the transfemoral route due to their experience with percutaneous coronary intervention. However, iliofemoral complications are the most common vascular complications in transfemoral TAVI. These complications include iliofemoral dissection, iliofemoral rupture, access site infection, stenosis, thrombosis, or occlusion, pseudoaneurysms, and femoral bleeding. To avoid these complications, a surgical cut-down was often performed in initial studies. A planned surgical cut-down can be performed at the beginning of the procedure to allow visualization and selection of the ideal puncture site and control of the artery above and below the puncture. Alternatively, a percutaneous puncture is performed and the artery is exposed for closure only. More recently, operators utilized percutaneous closure devices. Our study showed that with a fully percutaneous procedure utilizing percutaneous closure with two ProGlides or one ProStar, low vascular complication rates can be achieved. Careful patient selection, and screening with CT angiography or fluoroscopic angiography were used to identify patients at high risk of complications. Such complications occurred more often if the minimal artery diameter was smaller than the sheath external diameter, and in the presence of moderate or severe calcification. With the available alternative access routes (transaxillary, transapical, transaortic), such patients should not undergo transfemoral TAVI.

5. Long-term outcomes after transcatheter aortic valve replacement

Since its introduction, the number of TAVI procedures was growing quickly world-wide. In 2012, it was estimated that in third-world countries, 20-50% of patients with severe aortic stenosis now undergo TAVI. Despite the growing popularity of TAVI, previous reports have focused on short- and mid-term outcomes, while little was known about longer-term outcomes. A few reports have investigated outcome up to 3 years[31, 54]. From these reports, it was known that with current patient selection, median survival after TAVI was about 3 years. Accelerated *in-vitro* testing showed that valves may last up to 15 years. In the early series, the high mortality rate was unlikely due to valve deterioration, but more likely due to the types of patients undergoing TAVI. Another important issue was and still is the occurrence of strokes. In the PARTNER trial, TAVI has been associated with higher rates of strokes and transient ischemic attacks than surgery, although the combined endpoint of strokes and death was non-significantly lower with TAVI compared to surgical AVR[7]. By analyzing long-term outcome, we also looked at the timing and type of strokes. We aimed to answer the following questions:

- Do transcatheter aortic valves last 5 years or are there signs of structural valve degeneration?
- Are there factors that predict long-term survival?
- What is the long-term stroke rate?

We analyzed 5 year outcome of the initial 111 patients undergoing TAVI at St. Paul's Hospital, Vancouver, British Columbia from January 2005 to March 2007[55]. Patients with unsuccessful valve implantation or who died within 30 days were excluded from the analysis, leaving 88 patients who were assessed. Median survival time after TAVI was 3.4 years (95% CI 2.5, 4.4 years) and survival rates at 1-5 years were 83%, 74%, 53%, 42%, and 35%, respectively. Median survival time for patients with and without COPD was 2.3 and 3.9 years, respectively. Median survival time for patients with ≥ moderate PAR and mild/trivial/no PAR was 1.7 and 3.4 years. Mean aortic valve gradient decreased from 46 to 10 mmHg post TAVI, and was 11.8 mmHg after five years ($p = 0.06$ for post-TAVI trend). Mean aortic valve area increased from 0.62 to 1.67 cm2 post TAVI, and was 1.4 cm2 at five years ($p<0.01$ for post-TAVI trend).

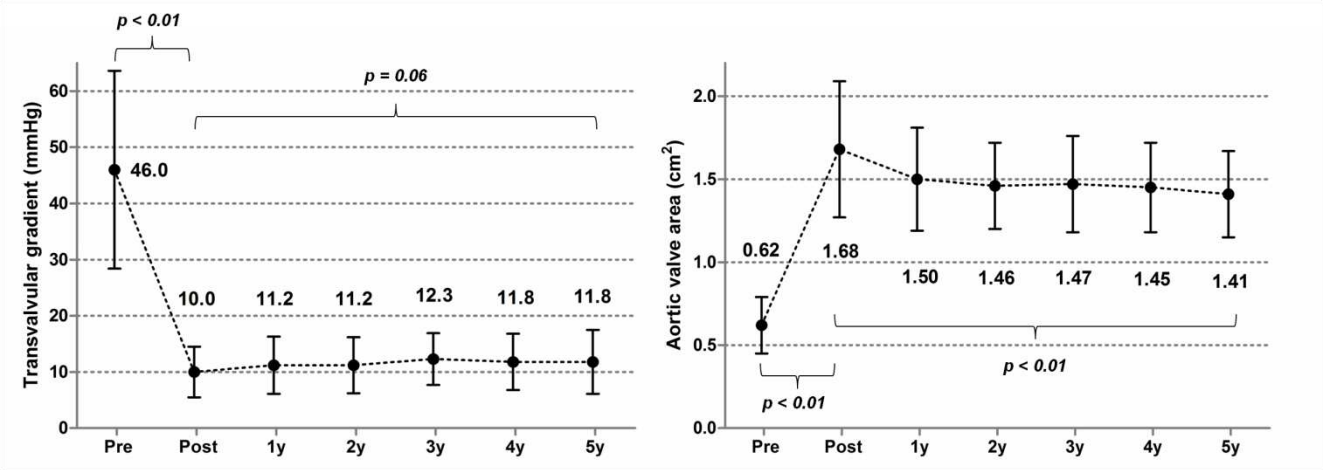

Figure 13. Mean gradients and aortic valve area remained stable with only marginal increase in gradient and mild decrease in valve area over time. (Toggweiler et al., *J Am Coll Cardiol* 2012;61:413-419)

Up to 4 years, no patient had signs of structural valve deterioration, but at 5 years, 3 patients had moderate prosthetic valve dysfunction (moderate transvalvular regurgitation in one, moderate stenosis in one (aortic valve area 1.2 cm^2, mean gradient 26 mmHg), and moderate mixed disease in one (aortic valve area 1.1 cm^2, mean gradient 23 mmHg). However, no patient developed severe stenosis or severe regurgitation and no patient required re-operation.

During the observation period, a total of 6 ischemic and 4 hemorrhagic major or fatal strokes occurred. Cumulative major ischemic stroke rate at 1-5 years was 3.6%, 5.2%, 7.3%, 7.3% and 9.7%, respectively, and 3/6 (50%) of ischemic strokes were fatal. Cumulative major hemorrhagic stroke rate at 1-5 years was 2.8%, 4.4%, 4.4%, 7.3%, and 7.3%, respectively, and 2/4 (50%) of hemorrhagic strokes were fatal.

To put these findings in perspective, it is important to remember that these patients represented the first in-human experience with transfemoral and transapical TAVI in truly inoperable patients explaining the relatively poor long-term survival. However, hemodynamics were excellent and signs of moderate prosthetic valve failure were observed in only 3.4% of patients after 5 years.

Cumulative ischemic stroke rate at 5 years was 9.7%, indicating an annual risk of ischemic strokes of about 2%. At the same time, cumulative major hemorrhagic stroke rate at 5 years was 7.3%. Of note, atrial fibrillation was present in 60% of these events indicating that atrial fibrillation may cause ischemic strokes (thromboembolism) and hemorrhagic strokes (bleeding due to antithrombotic therapy).

Stroke type	Days post TAVI	Risk factors	Antiplatelet regimen	Outcome
Ischemic	2	Atrial fibrillation	Aspirin, clopidogrel	Patient survived
Ischemic	54	None	Aspirin, clopidogrel	Patient died
Ischemic	119	Atrial fibrillation	Warfarin	Patient died.
Ischemic	637	None	Aspirin	Patient survived
Ischemic	902	Carotid stenosis	Aspirin	Patient died
Ischemic	1674	Atrial fibrillation	Aspirin, clopidogrel	Patient survived
Hemorrhagic	203	Atrial fibrillation	Warfarin, aspirin	Patient died
Hemorrhagic	211	Atrial fibrillation	Warfarin	Patient died
Hemorrhagic	608	Atrial fibrillation	Warfarin	Patient survived
Hemorrhagic	1405	None	Aspirin, clopidogrel	Patient survived

Table 1. Ischemic and hemorrhagic strokes up to 5 years post TAVI. (Toggweiler et al., *J Am Coll Cardiol* 2012;61:413-419)

Based on our results, we were confident that transcatheter valves will last longer than 5 years and that patients with a longer life-expectancy will have long-term benefits from a durable valve.

6. Perspective

Further refinement of the procedure and current developments focus on minimizing vascular complications, reducing the risk for cerebrovascular accidents, improving paravalvular sealing, and facilitating accurate prosthesis implantation. Some of these issues may be addressed by next-generation valves that currently undergo early clinical evaluation. Most of these valves are constructed of self-expanding nitinol which offers the potential for recapture, repositioning, and removal, if required[56].

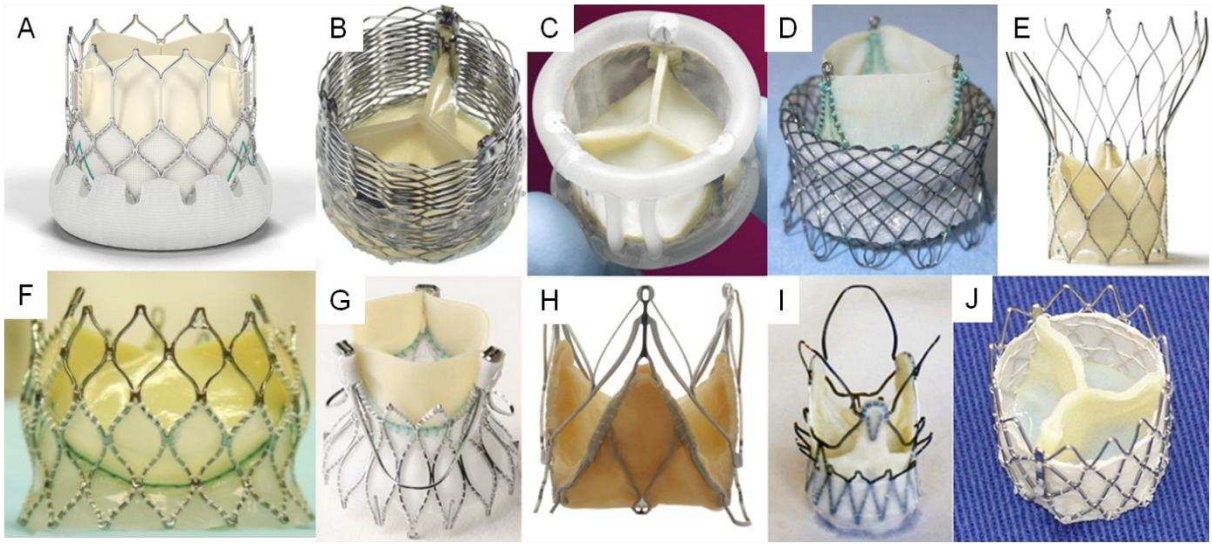

Figure 14. Next generation transcatheter heart valves. A: S3 (Edwards Lifesciences),B: Lotus Valve (Boston Scientific), C: Direct Flow (Direct Flow Medical), D: HLT System (Heart Leaflet Technologies), E: Portico (St. Jude Medical), F: Centera (Edwards Lifesciences), G: Engager (Medtronic), H: JenaValve (JenaValve Technology), I: Accurate (Symetis), J: Inovare (Braile Biomedica).

The S3 valve (Edwards Lifesciences, Irvine, USA) has a delivery system that is inserted through a 14 F expandable sheath which facilitates a fully percutaneous implantation in a broader range of patients. Furthermore, the valve has a parachute-like outer polyethylene terephthalate (PET) skirt that enhances paravalvular sealing[57].

Unlike other valves, the Direct Flow aortic valve (Direct Flow Medical, Santa Rosa, USA) is not based on a metallic stent frame technology. To deploy the valve, the lower ventricular and the upper aortic rings are inflated with 50%/50% saline/contrast. If required, repositioning can be performed after partial deflation, or the valve can be removed completely and exchanged for a valve of a different size. When correct position is achieved, the saline/contrast mix is

exchanged with a polymer which is firmly gelled within 90 minutes and fully cured within 24 hours[58].

The Portico valve (St. Jude Medical Inc., St. Paul, USA), is a self-expanding valve very similar to a CoreValve. However, the Portico valve allows partial or complete recapture enabling the valve to be repositioned or removed. Only the 23 mm device is currently available[59].

The Centera valve (Edwards Lifesciences, Irvine, USA) is a relatively short self-expanding valve that does not extend into the ascending aorta for self-alignment or anchoring. The inflow is non-tubular flared, with a narrower annular segment and a larger diameter outflow. The idea behind this shape is to facilitate self-seating in the aortic annulus and reduce paravalvular regurgitation. The Centera valve can be deployed and if necessary recaptured using a single hand operated motorized delivery system[60].

The self-expanding Acurate valve (Symetis, Ecublens, Switzerland) has three stabilization arms meant to stabilize the valve in the ascending aorta. The valve has an upper crown that provides tactile feedback during positioning. Similar to a 'hook concept', optimal valve position is achieved by applying slight tension on the delivery system and thereby on the upper crown[61].

With improved equipment, and more experience, there is no doubt that rates of mortality, paravalvular regurgitation, strokes, and vascular complications will decrease. Compared to open heart surgery, TAVI is less invasive, allows earlier patient ambulation, and requires a shorter recovery and rehabilitation period. There is no doubt that the indication for TAVI will be extended and that TAVI will be applied in a broader spectrum of patients with severe aortic stenosis or regurgitation.

7. References

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9. Appendix

Appendix 1 **Stefan Toggweiler**, Robert H. Boone, Josep Rodés-Cabau, Karin H. Humphries, May Lee, Luis Nombela-Franco, Rodrigo Bagur, Alexander B. Willson, Ronald K. Binder, Ronen Gurvitch, Jasmine Grewal, Robert Moss, Brad Munt, Christopher R. Thompson, Melanie Freeman, Jian Ye, Anson Cheung, Eric Dumont, David A. Wood, John G. Webb.

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Appendix 2 Karin H. Humphries, **Stefan Toggweiler**, Josep Rodés-Cabau, Luis Nombela-Franco, Eric Dumont, David A. Wood, Alexander B. Willson, Ronald K. Binder, Melanie Freeman, May K. Lee, Min Gao, Mona Izadnegahdar, Jian Ye, Anson Cheung, John G. Webb.

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Appendix 3 Alexander B. Willson, John G. Webb, Troy M. LaBounty, Stephan Achenbach, Robert Moss, Miriam Wheeler, Christopher Thompson, James J. Min, Ronen Gurvitch, Bjarne L. Norgaard, Cameron J. Hague, **Stefan Toggweiler**, Ronald Binder, Melanie Freeman, Rohan Poulter, Steen Poulsen, David A. Wood, Jonathon Leipsic.

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Appendix 4 **Stefan Toggweiler**, Ronen Gurvitch, Jonathon Leipsic, David A. Wood, Alexander B. Willson , Ronald K. Binder, Anson Cheung, Jian Ye, John G. Webb.

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Appendix 5 **Stefan Toggweiler**, Karin H. Humphries, May Lee, Ronald K. Binder, Robert R. Moss, Melanie Freeman, Jian Ye, Anson Cheung, David A. Wood, John G. Webb.

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